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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(72) Inventors; and

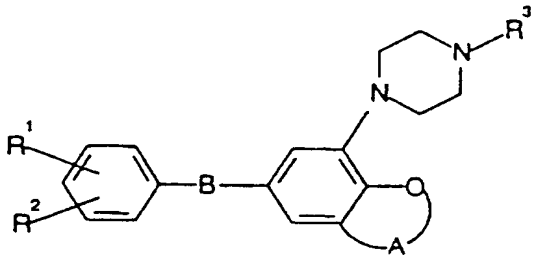
(75) Inventors/Applicants *(for US only)*: JOINER, Graham, Francis [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB). GASTER, Laramie, Mary [GB/GB]; SmithKline Beecham Pharmaceuticals, Coldharbour Road, The Pinnacles, Harlow, Essex CM19 5AD (GB).

(74) Agent: FLORENCE, Julia; SmithKline Beecham, Corporate Intellectual Property, SB House, Great West Road, Brentford, Middlesex TW8 9BD (GB).

(54) Title: BENZANILIDE DERIVATIVES AS 5HT-1D RECEPTOR ANTAGONISTS

(57) Abstract

Amide derivatives of formula (I) or a salt thereof, in which R^1 is halogen, C_{3-6}cycloalkyl, optionally substituted phenyl or an optionally substituted 5-7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur; R^2 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, acyl, nitro, trifluoromethyl or cyano; R^3 is hydrogen or C_{1-6}alkyl; and A is $-(CR^4R^5)_m-$ or $-O(CR^4R^5)_n-$ where R^4 and R^5 are independently hydrogen or C_{1-6}alkyl, m is 2, or 3; n is 1, 2 or 3 and B is CONH or NHCO, processes for their preparation, and pharmaceutical compositions containing them.



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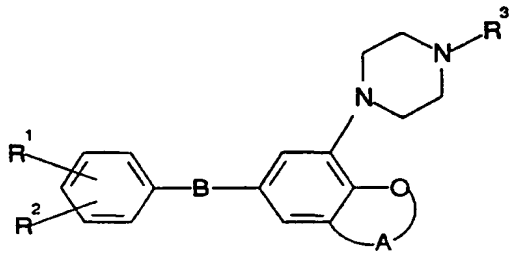
BENZANILIDE DERIVATIVES AS 5HT-1D RECEPTOR ANTAGONISTS

The present invention relates to novel amide derivatives, processes for their preparation, and pharmaceutical compositions containing them.

EPA 0 533 266/7/8 disclose a series of benzanilide derivatives which are said to possess $5HT_{1D}$ receptor antagonist activity. These compounds are said to be of use in the treatment of various CNS disorders.

A structurally distinct class of compounds have now been discovered and have been found to exhibit $5HT_{1D}$ antagonist activity. In a first aspect, the present invention therefore provides a compound of formula (I) or a salt thereof:



(I)

in which

R^1 is halogen, C_{3-6}cycloalkyl, optionally substituted phenyl or an optionally substituted 5-7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;

R^2 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, acyl, nitro, trifluoromethyl or cyano;

R^3 is hydrogen or C_{1-6}alkyl; and

A is $-(CR^4R^5)_m-$ or $-O(CR^4R^5)_n-$ where R^4 and R^5 are independently hydrogen or C_{1-6}alkyl, m is 2, or 3;

n is 1, 2 or 3 and

B is CONH or NHCO.

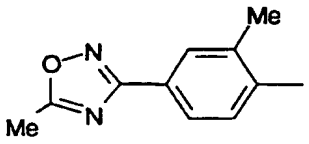
The group R^1 can be an aromatic or saturated heterocyclic ring. When R^1 is an aromatic heterocyclic ring, examples of such rings include thienyl, furyl, pyrrolyl, triazolyl, diazolyl, imidazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrimidyl and pyrazinyl. When R^1 is a saturated ring examples include piperidine, morpholine and piperazine rings. The group R^1 can be linked to the remainder of the molecule via a carbon atom or, when present, a nitrogen atom. Examples of R^1 C_{3-6}cycloalkyl groups include cyclohexyl.

Preferably the group R^1 is attached to the 4-position of the phenyl ring, that is to say, para to the amide group. Optional substituents for R^1, of which more than one can be present, include halogen, C_{1-6}alkyl, C_{1-6}alkoxy, hydroxy, cyano, nitro, amino, CO_2R^6

where R^6 is hydrogen or C_{1-6}alkyl or $CONR^7R^8$ where R^7 and R^8 are hydrogen or C_{1-6}alkyl.

The group R^1 can also be an optionally substituted phenyl group, in particular a phenyl group disubstituted by C_{1-6}alkyl and an optionally substituted 5 to 7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur. Preferred 5 to 7-membered heterocyclic rings include those listed above. Preferred substituents for such rings include C_{1-6}alkyl, in particular methyl.

Preferably R^1 is halogen, pyridyl or a phenyl group disubstituted by a C_{1-6}alkyl group and an optionally substituted 5-7 membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur. More preferably R^1 is a phenyl group disubstituted by methyl and an optionally substituted oxadiazolyl group, in particular an oxadiazolyl group substituted by C_{1-6}alkyl. Most preferably R^1 is a group of formula:



Suitably R^2 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy or nitro. Preferably R^2 is hydrogen, methyl or nitro, most preferably hydrogen.

Suitably R^3 is hydrogen or C_{1-6}alkyl. Preferably R^3 is hydrogen or methyl.

Preferably A is CH_2CH_2 or OCH_2CH_2.

Preferably B is CONH.

Particularly preferred compounds include:

4-bromo-3-methyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzamide,

4-bromo-3-methyl-N-[7-(piperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzamide,

4-bromo-3-methyl-N-[5-(4-methylpiperazin-1-yl)-1,4-benzodioxan-7-yl]benzamide,

4-(4-pyridyl)-3-methyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzamide,

4-(4-pyridyl)-3-methyl-N-[5-(4-methylpiperazin-1-yl)-1,4-benzodioxan-7-yl]benzamide,

N-[7-(4-methylpiperazin-1-yl)-2,3-dihydro-2-methylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide, or

N-[7-(4-methylpiperazin-1-yl)-2,3-dihydro-2,2-dimethylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

N-[7-(Piperazin-1-yl)-2,3-dihydro-2,2-dimethylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,

4-Bromo-3-methyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydro-2,2-dimethylbenzofuran-5-yl]benzamide,

N-[7-(piperazin-1-yl)-2,3-dihydro-2-methylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
4-Bromo-3-methyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydro-2-methylbenzofuran-5-yl]benzamide,
N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
N-[7-(Piperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
or a pharmaceutically acceptable salt thereof.

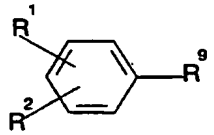
C_{1-6}alkyl groups, whether alone or as part of another group, may be straight chain or branched.

Preferred salts of the compounds of formula (I) are pharmaceutically acceptable salts. These include acid addition salts such as hydrochlorides, hydrobromides, phosphates, acetates, fumarates, maleates, tartrates, citrates, oxalates, methanesulphonates and p-toluenesulphonates.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and the mixtures thereof including racemates. Tautomeric forms of compounds of formula (I) and mixtures thereof also form an aspect of the invention.

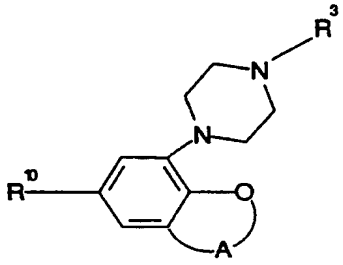
In a further aspect the present invention provides a process for the preparation of a compound of formula (I) which comprises.

(a) reaction of a compound of formula (II):



(II)

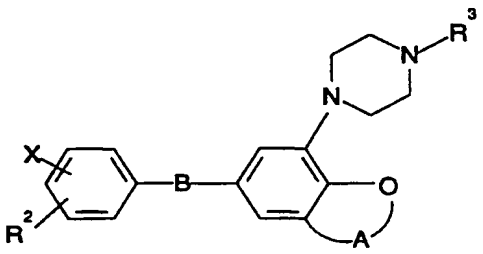
with a compound of formula (III):



(III)

in which R^1, R^2, R^3 and A are as defined in formula (I) and R^9 and R^{10} contain the appropriate functional group(s) necessary to form the B moiety;

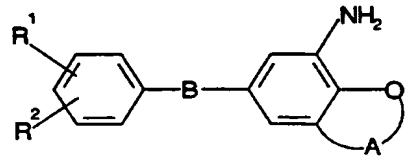
(b) reaction of a compound of formula (IV):



(IV)

in which R^2, R^3, A and B are as defined in formula (I) and X is a leaving group with a nucleophile R^1 where R^1 is as defined in formula (I); or

(c) reaction of a compound of formula (V):



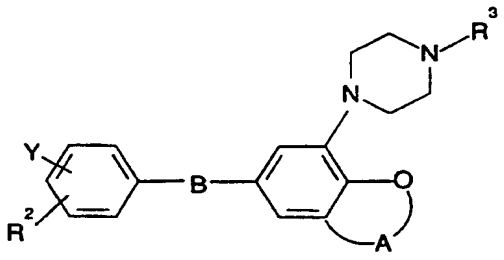
(V)

in which R^1, R^2, A and B are as defined in formula (I) with a compound of formula (VI):

$$R^3N(CH_2CH_2Hal)_2 \qquad (VI)$$

in which R^3 is as defined in formula (I) and Hal is halogen, or

(d) reaction of a compound of formula (VII):



(VII)

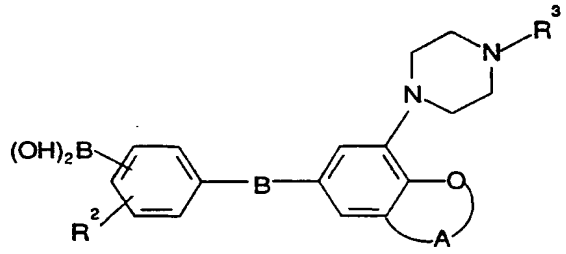
in which R^2, R^3, A and B are as defined in formula (I) and Y is halogen or a group $-OSO_2CF_3$ with a compound of formula (VIII):

$$R^1B(OH)_2$$

(VIII)

in which R^1 is as defined in formula (I), or

(e) reaction of a compound of formula (IX):



(IX)

in which R^2, R^3, A and B are as defined in formula (I) with a compound of formula (X):

$$R^1Y$$

(X)

in which R^1 is as defined in formula (I) and Y is as defined in formula (VII),

and optionally thereafter:

- converting a compound of formula (I) into another compound of formula (I)
- forming a pharmaceutically acceptable salt.

Suitably one of R^9 or R^{10} is an activated carboxylic acid derivative, such as an acyl halide or acid anhydride, and the other is an amine group. Activated compounds of formulae (II) or (III) can also be prepared by reaction of the corresponding carboxylic acid with a coupling reagent such as carbonyldiimidazole, dicyclohexylcarbodiimide or diphenylphosphorylazole. Preferably R^9 or R^{10} is a group COL where L is halo, particularly chloro.

A compound of formulae (II) and (III) are typically reacted together in an inert organic solvent such as DMF, THF or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine, pyridine or aqueous sodium hydroxide. Compounds of formulae (II) and (III) can be prepared from the corresponding carboxylic acids using standard procedures. For example acid chlorides can be prepared by reaction with phosphorous pentachloride, oxalyl chloride or thionyl chloride. Acid anhydrides can be prepared by reaction with a suitable acid anhydride, for example trifluoroacetic anhydride.

Reaction of a compound of formula (IV) with a nucleophile R^1 is preferably carried out in a suitable solvent such as dimethylformamide in the presence of a strong base such as sodium hydride. Preferably the leaving group X is halo, in particular fluoro. Preferably the group R^2 is an electron withdrawing group, for example nitro, $COCH_3$ or cyano, in the ortho or para-positions relative to the group X.

Reaction of a compound of formula (V) with a compound of formula (VI) is suitably carried out in an alcohol or nitrile solvent with an optional base or, alternatively, in a non-polar solvent such as chlorobenzene in the absence of base. Suitably, the reactions are carried out at ambient or elevated temperature, preferably at the reflux temperature of the reaction mixture.

Reaction of compounds of formula (VII) and (VIII) and reaction of compounds of formulae (IX) and (X) can be carried out in the presence of a transition metal catalyst such as $Pd(PPh_3)_4$ in a solvent such as an ether in the presence of a base such as an alkali metal carbonate or bicarbonate, for example sodium carbonate or bicarbonate, at ambient or elevated temperature.

Intermediate compounds of formulae (III), (IV), (V), (VI), (VII), (VIII), (IX) and (X) are commercially available or can be prepared using standard procedures. For example certain compounds can be prepared using similar procedures to those outlined in EPA 533266/7/8.

It will be appreciated to those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures, for example when the group R^3 is a hydrogen atom. Standard protection and deprotection techniques can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. These groups can be removed by conventional

procedures.

Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection is achieved using standard conditions.

$5HT_{1D}$ Antagonists, and in particular the compounds of the present invention, are expected to be of use in the treatment of CNS disorders such as mood disorders, including depression, seasonal effective disorder and dysthymia; anxiety disorders, including generalised anxiety, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder; memory disorders, including dementia, amnestic disorders and age-associated memory impairment; and disorders of eating behaviours, including anorexia nervosa and bulimia nervosa. Other CNS disorders include Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

$5HT_{1D}$ Antagonists, and in particular compounds of the present invention, may also be of use in the treatment of endocrine disorders such as hyperprolactinaemia, in the treatment of vasospasm (particularly in the cerebral vasculature) and hypertension, as well as disorders in the gastrointestinal tract where changes in motility and secretion are involved. They may also be of use in the treatment of sexual dysfunction.

Therefore, the present invention, provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in therapy.

The present invention also provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment of the aforementioned disorders.

In another aspect the invention provides the use of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of the aforementioned disorders.

In a further aspect the invention provides a method of treating the aforementioned disorders which comprises administering an effective amount to a patient in need of such treatment of a compound of general formula (I) or a pharmaceutically acceptable salt or solvate thereof.

In particular the invention provides a compound of general formula (I) or a physiologically acceptable salt or solvate thereof for use in the treatment or prophylaxis of depression.

It will be appreciated by those skilled in the art that the compounds according to the invention may advantageously be used in conjunction with one or more other therapeutic agents, for instance, different antidepressant agents.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a

pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention.

Description 1
2,3-dihydrobenzofuran-7-carboxylic acid (D1)

Following the procedure outlined in EP-A-307172, Example 15, 2,3-dihydrobenzofuran (10.73g) was converted to the title compound (D1) (6g, 41%).

^{1}H NMR 250 MHz ($CDCl_3$) δ : 8.76 (brs, 1H), 7.82 (d, 1H), 7.42 (d, 1H), 6.95 (t, 1H), 4.8 (t, 2H), 3.3 (t, 2H)

Description 2
7-(trifluoroacetylamino)-2,3-dihydrobenzofuran (D2)

2,3-dihydrobenzofuran-7-carboxylic acid (D1) (1.42g) was dissolved in a mixture of trifluoroacetic acid (50 ml) and trifluoroacetic anhydride (10 ml). After stirring at room temperature for 1.5 h, the mixture was cooled to 0° C and treated portionwise with sodium azide (1.4 eq = 788 mg), then stirred at room temperature for 2 days under argon. The mixture was evaporated under reduced pressure, and the residue partitioned between $CHCl_3$ and water. The organic phase was washed with K_2CO_3 (aq), dried (Na_2SO_4) and the solvent evaporated under reduced pressure, to give the title compound (1.64g, 82%) as an off-white crystalline material.

^{1}H NMR 250 MHz ($CDCl_3$) δ : 7.85-8.2 (m, 2H), 7.05 (d, H), 6.89 (t, H), 4.65 (t, 2H), 3.28 (t, 2H)

Description 3
7-amino-2,3-dihydrobenzofuran (D3)

A solution of 7-(trifluoroacetylamino)-2,3-dihydrobenzofuran (D2) (1.6g) in methanol (30 ml) and 10% NaOH (3 ml) was heated to reflux for 24 h. The mixture was evaporated under reduced pressure and partitioned between ethyl acetate and water. The organic phase was dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give the title compound (900 mg, 96%) as a pale orange oil, which crystallised on standing.

^{1}H NMR 200 MHz ($CDCl_3$) δ : 6.44-6.75 (m, 3H), 4.57 (t, 2H), 3.55 (br s, 2H), 3.2 (t, 2H)

Description 4
7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran (D4)

A solution of 7-amino-2,3-dihydrobenzofuran (D3) (2g) in chlorobenzene (15 ml) was treated with mechlorethamine hydrochloride (2.85 g) and the mixture refluxed overnight under Argon. The solvent was evaporated under reduced pressure and the residue was dissolved in 1-butanol (30 ml) and treated with Na_2CO_3 (6.28 g). After refluxing under Argon for a further 24 h, the solvent was evaporated under reduced pressure and partitioned between ethyl acetate and water. Organic phase was dried (Na_2SO_4) and solvent evaporated under reduced pressure to give the title compound as a red oil (1.32 g, 41%).

^1H NMR 250 MHz ($CDCl_3$) δ :6.69-7.0 (m, 3H), 4.6 (t, 2H), 3.05-3.35 (m, 6H), 2.52-2.73 (m, 4H), 2.35 (s, 3H)

Description 5
7-(4-methylpiperazin-1-yl)-5-nitro-2,3-dihydrobenzofuran (D5)

Potassium nitrate (705 mg) was added portionwise over ½h to a solution of 7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran (D4) (1.32 g) in concentrated sulphuric acid (16 ml) at room temperature. The resulting solution was stirred for a further ½ h, then added to ice (40 g), basified with 5N NaOH, and extracted into ethyl acetate. The organic phase was dried (Na_2SO_4) and the solvent evaporated under reduced pressure to give the title compound (847 mg, 53%) as an orange, crystalline solid.

^1H NMR 250 MHz ($CDCl_3$) δ :7.79 (s, 1H), 7.64 (s, 1H), 4.78 (t, 2H), 3.1-3.38 (m, 6H), 2.5-2.7 (m, 4H), 2.36 (s, 3H)

Description 6
7-(4-methylpiperazin-1-yl)-5-amino-2,3-dihydrobenzofuran (D6)

A solution of 7-(4-methylpiperazin-1-yl)-5-nitro-2,3-dihydrobenzofuran (D5) (845 mg) in ethanol (50 ml) was hydrogenated over 10% Palladium on charcoal (0.5 g) at atmospheric pressure and room-temperature for 1 h. The catalyst was removed by filtration through kieselguhr, and the filtrate evaporated under reduced pressure to give the title compound (741 mg, 99%).

^1H NMR 250 MHz ($CDCl_3$) δ : 6.25 (s, 1H), 6.1 (s, 1H), 4.53 (t, 2H), 2.5-3.3 (m, 12H),

2.35 (s, 3H).

Description 7
7-Nitro-1,4-benzodioxan-5-carboxylic acid (D7)

Benzodioxan-5-carboxylic acid (prepared as described by E.A.Watts, in Azabicycloalkylbenzamides and pharmaceutical compositions containing them, EP 82-303057 June 1982) (15 g) was dissolved in a mixture of glacial acetic acid (67 ml) and acetic anhydride (67 ml). The solution was heated to 40° C and treated with a solution of fuming nitric acid (13 ml) in acetic acid (13 ml) at a rate such that the temperature was maintained at 45-50° C with occasional ice/water cooling. The mixture was stirred at 50°-53° C for 2 days, then cooled and filtered to give the title compound as a white powder (4.09 g, 22%).

^{1}H NMR 250 MHz (DMSO-d6) δ : 8.09 (s, 1H), 7.85 (s, 1H), 4.28-4.59 (m, 4H).

Description 8
7-amino-1,4-benzodioxan-5-carboxylic acid (D8)

A solution of 7-nitro-1,4-benzodioxan-5-carboxylic acid (D7) (2.81g) in ethanol (100 ml) was hydrogenated over 10% Palladium on charcoal (750 mg) for 20 h. The catalyst was removed by filtration through kieselguhr and the filtrate evaporated under reduced pressure to give the title compound as a white solid (1.96 g, 81%)

^{1}H NMR 200 MHz (DMSO-d6) δ : 6.5 (s, 1H), 6.26 (s, 1H), 4.03-4.3 (m, 4H), 3.4 (br s, 2H).

Description 9
4-bromo-3-methyl-N-[5-carboxy-1,4-benzodioxan-7-yl]benzamide (D9)

Following the method outlined in Example 1, 7-amino-1,4-benzodioxan-5-carboxylic acid (D8) (1.96 g) was converted to the title compound as an off-white powder (3.19 g, 81%).

^{1}H NMR 250 MHz (DMSO-d6) δ : 10.19 (s, 1H), 7.96 (s, 1H), 7.72 (s, 2H), 7.36 (s, 1H), 7.30 (s, 1H), 4.12-4.25 (m, 4H), 2.42 (s, 3H)

Description 10
4-Bromo-3-methyl-N-[5-(trifluoroacetylamino)-1,4-benzodioxan-7-yl]benzamide (D10)

Following the method outlined in description 2, 4-bromo-3-methyl-N-[5-carboxy-1,4-benzodioxan-7-yl]benzamide (D9) (1.0 g) was converted to the title compound (739 mg, 63%).

^{1}H NMR 200 MHz (DMSO-d6) δ : 10.89 (s, 1H), 10.23 (s, 1H), 7.92 (s, 1H), 7.56-7.8 (m, 2H), 7.42 (s, 1H), 7.39 (s, 1H), 4.19-4.46 (m, 4H), 2.42 (s, 3H)

Description 11
4-bromo-3-methyl-N-[5-amino-1,4-benzodioxan-7-yl]benzamide (D11)

Following the method outlined in description 3, 4-bromo-3-methyl-N-[5-(trifluoroacetylamino)-1,4-benzodioxan-7-yl]benzamide (D10) (1.85 g) was converted to the title compound (137 mg).

^{1}H NMR 250 MHz ($CDCl_3$) δ :7.7 (s, 1H), 7.55-7.65 (m, 2H), 7.45 (d, 1H), 6.8 (s, 1H), 6.5 (s, 1H), 4.2- 4.38 (m, 4H), 3.81 (br s, 2H), 2.44 (s, 3H).

Description 12
2,3-dihydro-2-methylbenzofuran-7-carboxylic acid (D12)

Following the procedure outlined in EP-A-307172, Example 15, 2,3-dihydro-2-methylbenzofuran (10.62g) was converted to the title compound (7.33g, 52%).

^{1}H NMR 250MHz ($CDCl_3$) δ : 7.82 (d, 1H), 7.38 (d, 1H), 6.95 (t, 1H), 5.3-5.1 (m, 1H), 3.5-3.3 (m, 1H), 3.0-2.8 (m, 1H), 1.58 (d, 3H)

Description 13
7-(trifluoroacetylamino)-2,3-dihydro-2-methylbenzofuran (D13)

Following the procedure outlined in description 2, 2,3-dihydro-2-methylbenzofuran-7-carboxylic acid (D12) (7.33g) was converted to the title compound (8.36g, 83%).

^{1}H NMR 200 MHz ($CDCl_3$) δ : 8.08-7.8 (m, 2H), 7.01 (d, 1H), 6.87 (t, 1H), 5.12-4.92 (m, 1H), 3.46-3.29 (m, 1H), 2.97-2.8 (m, 1H), 1.5 (d, 3H).

Description 14
7-amino-2,3-dihydro-2-methylbenzofuran (D14)

Following the procedure outlined in description 3, 7-(trifluoroacetylamino)-2,3-dihydro-2-methylbenzofuran (D13) (8.36g) was converted to the title compound (4.83g, 95%)

^{1}H NMR 200 MHz ($CDCl_3$) δ : 6.74-6.45 (m, 3H), 5.01-4.81 (m, 1H), 3.76-3.2 (m, 3H), 2.9-2.71 (m, 1H), 1.48 (d, 3H).

Description 15
7-(4-methylpiperazin-1-yl)-2,3-dihydro-2-methylbenzofuran (D15)

A solution of 7-amino-2,3-dihydro-2-methylbenzofuran (D14) (4.83g) in 1-butanol (80 ml) was treated with mechlorethamine hydrochloride (12.5 g) and the mixture refluxed under argon for 24 h. Sodium carbonate (13.7 g) was added and reflux continued for 48h. The solvent was evaporated under reduced pressure and the residue was partitioned between 10% (aq) sodium hydroxide and dichloromethane. The organic phase was dried (Na_2SO_4) and the solvent removed under reduced pressure to give a residue which was chromatographed on silica, eluting with ethylacetate and n-pentane to give the title compound as an orange oil (4g, 53%)

^{1}H NMR 200 MHz ($CDCl_3$) δ : 6.86-6.65 (m, 3H), 5.05-4.84 (m, 1H), 3.37-3.0 (m, 5H), 2.9-2.73 (m, 1H), 2.69-2.51 (m, 4H), 2.35 (s, 3H), 1.5 (d, 3H).

Description 16
7-(4-methylpiperazin-1-yl)-5-nitro-2,3-dihydro-2-methylbenzofuran (D16)

Following the procedure outlined in description 5, 7-(4-methylpiperazin-l-yl)-2,3-dihydro-2-methylbenzofuran (D15) (4g) was converted to the title compound (2.81g, 59%)

^{1}H NMR 250 MHz ($CDCl_3$) δ : 7.75 (s, 1H), 7.64 (s, 1H), 5.25-5.04 (m, 1H), 3.45-3.05 (5H), 2.94-2.8 (m, 1H), 2.72-2.51 (m, 4H), 2.37 (s, 3H), 1.55 (d, 3H)

Description 17
5-amino-7-(4-methylpiperazin-1-yl)-2,3-dihydro-2-methylbenzofuran (D17)

Following the procedure outlined in description 6, 7-(4-methylpiperazin-1-yl)-5-nitro-2,3-dihydro-2-methylbenzofuran (D16) (2.81g) was converted to the title compound (2.57g, quantitative).

^{1}H NMR 250MHz ($CDCl_3$) δ : 6.2 (s, 1H), 6.1 (s, 1H), 5.0-4.78 (m, 1H), 3.54-2.89 (m, 7H), 2.81-2.49 (m, 5H), 2.35 (s, 3H), 1.46 (d, 3H)

Description 18
7-(4-methylpiperazin-1-yl)-2,3-dihydro-2,2-dimethylbenzofuran (D18)

Following the procedure outlined in description 15, 2,3-dihydro-2,2-dimethyl-7-benzofuranamine (4.93g) was converted into the title compound (2.48g, 33%)

^{1}H NMR 250 MHz ($CDCl_3$) δ : 6.85-6.65 (m, 3H), 3.29-3.09 (m, 4H), 2.98 (s, 2H), 2.7-2.51 (m, 4H), 2.34 (s, 3H), 1.49 (s, 6H).

Description 19
7-(4-methylpiperazin-1-yl)-5-nitro-2,3-dihydro-2,2-dimethylbenzofuran (D19)

Following the procedure outlined in description 5, 7-(4-methylpiperazin-1-yl)-2,3-dihydro-2,2-dimethylbenzofuran (D18) (2.48g) was converted to the title compound (1.46g, 50%)

^{1}H NMR 200 MHz ($CDCl_3$) δ : 7.72 (s, 1H), 7.61 (s, 1H), 3.29-3.14 (m, 4H), 3.05 (s, 2H), 2.65-2.52 (m, 4H), 2.35 (s, 3H), 1.52 (s, 6H)

Description 20
5-Amino-7-(4-methylpiperazin-1-yl)-2,3-dihydro-2,2-dimethylbenzofuran (D20)

Following the procedure outlined in description 6, 7-(4-methylpiperazin-1-yl)-5-nitro-2,3-dihydro-2,2-dimethylbenzofuran (D19) (1.46g) was converted to the title compound (1.06g, 81%)

^{1}H NMR 250 MHz ($CDCl_3$) δ : 6.19 (s, 1H), 6.11 (s, 1H), 3.25-3.04 (m, 4H), 2.9 (s, 2H), 2.68-2.51 (m, 4H), 2.35 (s, 3H), 1.45 (s, 6H)

Example 1

4-bromo-3-methyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzamide (E1)

4-bromo-3-methylbenzoic acid (690 mg) was refluxed for 1 h in thionyl chloride (10 ml), then cooled to room-temperature and evaporated under reduced pressure to leave the acid chloride. A solution of 7-(4-methylpiperazin-1-yl)-5-amino-2,3-dihydrobenzofuran (D6) (740 mg) in tetrahydrofuran (50 ml) was treated with a solution of the acid chloride (749 mg) in tetrahydrofuran (10 ml) and sodium hydroxide (0.26 g) in water (4 ml). The mixture was stirred for three days under Argon at room temperature, then the solvent was evaporated under reduced pressure, and the residue partitioned between ethyl acetate and water. The organic phase was dried (Na_2SO_4), the solvent evaporated under reduced pressure and the residue passed through a short silica (flash) column, eluting with methanol/ethyl acetate(1%-6%), to give the title compound (810 mg, 59%), mp 93-5° C.

^1H NMR 250 MHz ($CDCl_3$) δ :7.74 (s, 2H), 7.62 (d, 1H), 7.5 (d, 1H), 7.23 (s, 1H), 6.86 (s, 1H), 4.62 (t, 2H), 3.03-3.32 (m, 6H), 2.52-2.71 (m, 4H), 2.46 (s, 3H), 2.35 (s, 3H).

Example 2

4-bromo-3-methyl-N-[7-(piperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzamide hydrochloride (E2)

A solution of 4-bromo-3-methyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzamide (E1) (250 mg) in dry toluene (4 ml) was cooled to 0° C and treated with α-chloroethyl chloroformate (166 mg). The mixture was stirred at room temperature for 1h, and filtered through kieselguhr. The filtrate was evaporated under reduced pressure and the residue dissolved in a mixture of dry toluene (5 ml) and methanol (4 ml) and stirred at room temperature overnight. The solvents were evaporated under reduced pressure to leave the title compound as an orange solid (65 mg) mp 129-132° C°.

^1H NMR 250 MHz (DMSO-d6) δ : 10.15 (s, 1H), 9.25 (br s, 2H), 7.94 (s, 1H), 7.65-7.77 (m, 2H), 7.4 (s, 1H), 7.2 (s, 1H), 4.54 (t, 2H), 3.05-3.32 (m, 10H), 2.42 (s, 3H).

Example 3

4-bromo-3-methyl-N-[5-(4-methylpiperazin-1-yl)-1,4-benzodioxan-7-yl]benzamide (E3)

A solution of 4-bromo-3-methyl-N-[5-amino-1,4-benzodioxan-7-yl]benzamide (D11) (128

mg) in 1-butanol (2 ml) was treated with mechlorethamine hydrochloride (136 mg) and the mixture refluxed under Argon overnight. Na_2CO_3 (150 mg) was added and the mixture refluxed for a further 24 h under Argon. The mixture was partitioned between dichloromethane and 10% NaOH, the organic phase dried (Na_2SO_4) and the solvent evaporated under reduced pressure. Purification on preparative tlc plate (Si) eluting with 7.5% ethanol/chloroform gave the title compound as a tan foam (90 mg, 57%) mp 70-73° C.

^1H NMR 250 MHz ($CDCl_3$) δ :7.66-7.82 (m, 2H), 7.62 (d, 1H), 7.5 (d, 1H), 6.96 (s, 1H), 6.8 (s, 1H), 4.16-4.45 (m, 4H), 2.98-3.29 (m, 4H), 2.54-2.78 (m, 4H), 2.45 (s, 3H), 2.36 (s, 3H).

Example 4

4-(4-pyridyl)-3-methyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzamide (E4)

To a solution of 4-bromo-3-methyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzamide (E1) (300 mg) in dimethoxyethane (10 ml) was added successively, 4-pyridylboronic acid (146 mg), sodium carbonate (192 mg) in water (5 ml) and tetrakis(triphenylphospine)palladium (0) (50 mg). The mixture was stirred at reflux under argon for 40 h, diluted with water and extracted into chloroform. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure and the residue purified by column chromatography (silica) eluting with methanol and chloroform (1%-4%), to give the title compound (204 mg, 68%), mp 90-3° C.

^1H NMR 250 MHz ($CDCl_3$) δ : 8.7 (d, 2H), 7.7-8 (m, 3H), 7.22-7.4 (m, 4H), 6.91 (s, 1 H), 4.64 (t, 2H), 3.05-3.35 (m, 6H), 2.52-2.77 (m, 4H), 2.26-2.49 (m, 6H)

Example 5

4-(4-pyridyl)-3-methyl-N-[5-(4-methylpiperazin-1-yl)-1,4-benzodioxan-7-yl]benzamide (E5)

Following the method outlined in example 4, 4-bromo-3-methyl-N-[5-(4-methylpiperazin-1-yl)-1,4-benzodioxan-7-yl]benzamide (E3) (73 mg) was converted to the title compound, and purified on preparative tlc plate (SiO_2) eluting with 15% ethanol/chloroform (42 mg, 58%) mp 230° C+ (dec)

^1H NMR 250 MHz ($CDCl_3$) δ : 8.7 (d, 2H), 7.82 (s, 2H), 7.75 (d, 1H), 7.21-7.37 (m,

3H), 7.01 (s, 1H), 6.85 (s, 1H), 4.2-4.38 (m, 4H), 3.01-3.25 (m, 4H), 2.55-2.78 (m, 4H), 2.38 (s, 3H), 2.34 (s, 3H).

Example 6

N-[7-(4-methylpiperazin-1-yl)-2,3-dihydro-2-methylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide (E6)

2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-carboxylic acid (EP 0533 268A1) (200 mg) was heated under reflux in excess thionyl chloride (5 ml) under argon for 1 hr, and the excess thionyl chloride evaporated under reduced pressure. The resulting acid chloride was dissolved in tetrahydrofuran (25 ml) and treated with 5-amino-7-(4-methylpiperazin-1-yl)-2,3-dihydro-2-methylbenzofuran (D17) (176 mg) in tetrahydrofuran (10 ml), and a solution of sodium hydroxide (57 mg) in water (1 ml). The mixture was stirred at room temperature overnight then the solvent was evaporated under reduced pressure. The residue was partitioned between water and dichloromethane, the organic phase was dried (Na_2SO_4) and the solvent evaporated under reduced pressure, to give the title compound as a brown foam (339 mg, 91%).

^{1}H NMR 250 MHz ($CDCl_3$) δ : 8.06-7.86 (m, 4H), 7.8 (s, 1H), 7.45 (d, 2H), 7.34 (d, 1H), 7.25 (d, 1H), 6.86 (s, 1H), 5.06-4.88 (m, 1H), 3.38-3.0 (m, 5H), 2.9-2.74 (m, 1H), 2.69 (s, 3H), 2.65-2.51 (m, 4H), 2.39-2.26 (m, 6H), 1.5 (d, 3H).

Example 7

N-[7-(4-methylpiperazin-1-yl)-2,3-dihydro-2,2-dimethylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide (E7)

Following the procedure outlined in example 6, 5-amino-7-(4-methylpiperazin-1-yl)-2,3-dihydro-2,2-dimethylbenzofuran (D20) (186 mg) was converted to the title compound (258 mg, 68%)

^{1}H NMR 250 MHz ($CDCl_3$) δ : 8.06-7.89 (m, 4H), 7.81 (s, 1H), 7.45 (d, 2H), 7.35 (d, 1H), 7.25 (d, 1H), 6.84 (s, 1H), 3.3-3.09 (m, 4H), 3.0 (s, 2H), 2.75-2.5 (m, 7H), 2.41-2.22 (m, 6H), 1.49 (s, 6H).

Example 8

N-[7-(Piperazin-l-yl)-2,3-dihydro-2,2-dimethylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide hydrochloride (E8)

A solution of N-[7-(4-methylpiperazin-l-yl)-2,3-dihydro-2,2-dimethylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide (E7) (150 mg) in dichloromethane (20 ml) was cooled to 0° C and treated with α-chloroethyl chloroformate (0.04 ml) and diisopropylethylamine (0.55 ml). The mixture was refluxed for 3h, cooled and filtered through a short neutral alumina column eluting with dichloromethane, then ethyl acetate. The solvent was evaporated under reduced pressure, and the residual carbamate dissolved in methanol (10 ml) and stood overnight. The solvent was evaporated under reduced pressure to leave the title compound as a white powder (38 mg, 22%) Mp 175-180° C.

^{1}H NMR 250 MHz (CD_3OD) δ: 8.08-7.98 (m, 3H), 7.94 (d, 1H), 7.57-7.47 (m, 2H), 7.39 (d, 1H), 7.27 (s, 1H), 7.19 (s, 1H), 3.4 (s, 8H), 3.06 (s, 2H), 2.68 (s, 3H), 2.35 (s, 3H), 1.5 (s, 6H).

Example 9

4-Bromo-3-methyl-N-[7-(4-methylpiperazin-l-yl)-2,3-dihydro-2,2-dimethyl benzofuran-5-yl]benzamide (E9)

Following the procedure outlined in example 1, 5-amino-7-(4-methylpiperazin-l-yl)-2,3-dihydro-2,2-dimethylbenzofuran (D20) (300 mg) was converted to the title compound (230mg, 44%) Mp 81-83° C.

^{1}H NMR 200 MHz ($CDCl_3$) δ: 7.72 (br s, 2H), 7.61 (d, 1H), 7.50 (d, 1H), 7.19 (s, 1H), 6.8 (s, 1H), 3.18 (br s, 4H), 2.99 (s, 2H), 2.67-2.51 (m, 4H), 2.45 (s, 3H), 2.35 (s, 3H), 1.49 (s, 6H).

Example 10

N-[7-(piperazin-l-yl)-2,3-dihydro-2-methylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide hydrochloride (E10)

Following the procedure outlined in example 8, N-[7-(4-methylpiperazin-1-yl)-2,3-dihydro-2-methylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide (E6) (150 mg) was converted to the title compound (55 mg, 35%) Mp 150-155° C.

^{1}H NMR 250 MHz (DMSO-d6) δ: 10.19 (s, 1H), 9.22 (br s, 2H), 8.16-7.85 (m, 4H), 7.61-7.75 (m, 2H), 7.49-7.39 (m, 2H), 7.24 (s, 1H), 5.04-4.85 (m, 1H), 3.48-3.18 (m, 9H), 2.87-2.65 (m, 4H), 2.35 (s, 3H), 1.4 (d, 3H).

Example 11

4-Bromo-3-methyl-N-[7-(4-methylpiperazin-l-yl)-2,3-dihydro-2-methylbenzofuran-5-yl]benzamide (E11)

Following the procedure outlined in example 1, 5-amino-7-(4-methylpiperazin-l-yl)-2,3-dihydro-2-methylbenzofuran (D17) (230 mg) was converted to the title compound (399 mg, 97%) Mp 73-5° C.

^{1}H NMR 250 MHz ($CDCl_3$) δ: 7.84-7.44 (m, 4H), 7.2 (s, 1H), 6.82 (s, 1H), 5.08-4.89 (m, 1H), 3.39-3.02 (m, 5H), 2.92-2.75 (m, 1H), 2.69-2.52 (m, 4H), 2.47 (s, 3H), 2.35 (s, 3H), 1.5 (d, 3H).

Example 12

N-[7-(4-methylpiperazin-l-yl)-2,3-dihydrobenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide (E12)

Following the procedure outlined in example 6, 7-(4-methylpiperazin-l-yl)-5-amino-2,3-dihydrobenzofuran (D6) (166 mg) was converted to the title compound (358 mg, 98%) Mp 80-85° C.

^{1}H NMR 250 MHz ($CDCl_3$) δ: 8.08-7.89 (m, 4H), 7.82 (s, 1H), 7.51-7.41 (m, 2H), 7.35 (d, 1H), 7.3-7.24 (m, 1H), 6.9 (s, 1H), 4.64 (t, 2H), 3.3-3.08 (m, 6H), 2.75-2.5 (m, 7H), 2.35 (d, 6H).

Example 13

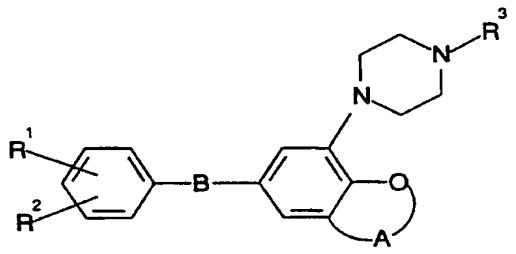
N-[7-(Piperazin-l-yl)-2,3-dihydrobenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide hydrochloride (E13)

Following the procedure outlined in example 8, N-[7-(4-methylpiperazin-l-yl)-2,3-dihydrobenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide (E12) (200 mg) was converted to the title compound (159 mg, 76%) Mp 159-162° C.

^{1}H NMR 250 MHz (CD_3OD) δ: 8.07-7.98 (m, 3H), 7.94 (d, 1H), 7.55-7.48 (m, 2H), 7.4 (d, 1H), 7.25 (s, 2H), 4.62 (t, 2H), 3.5-3.2 (m, 10H), 2.68 (s, 3H), 2.36 (s, 3H).

CLAIMS:

1. A compound of formula (I) or a salt thereof:

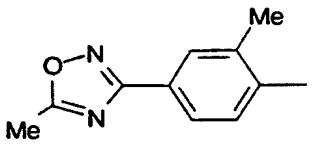


(I)

in which
R^1 is halogen, C_{3-6}cycloalkyl, optionally substituted phenyl or an optionally substituted 5-7-membered heterocyclic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur;
R^2 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, acyl, nitro, trifluoromethyl or cyano;
R^3 is hydrogen or C_{1-6}alkyl; and
A is $-(CR^4R^5)_m-$ or $-O(CR^4R^5)_n-$ where R^4 and R^5 are independently hydrogen or C_{1-6}alkyl, m is 2, or 3;
n is 1, 2 or 3 and
B is CONH or NHCO.

2. A compound according to claim 1 in which R^1 is halogen, pyridyl or a disubstituted phenyl group.

3. A compound according to claim 1 or 2 in which R^1 is:



4. A compound according to any one of claims 1 to 3 in which R^2 is hydrogen.

5. A compound according to any one of claims 1 to 4 in which R^3 is hydrogen or methyl.

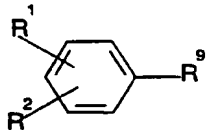
6. A compound according to any one of claims 1 to 5 in which A is CH_2CH_2 or OCH_2CH_2 and B is CONH.

7. A compound according to claim 1 which is

4-bromo-3-methyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzamide,
4-bromo-3-methyl-N-[7-(piperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzamide,
4-bromo-3-methyl-N-[5-(4-methylpiperazin-1-yl)-1,4-benzodioxan-7-yl]benzamide,
4-(4-pyridyl)-3-methyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]benzamide,
4-(4-pyridyl)-3-methyl-N-[5-(4-methylpiperazin-1-yl)-1,4-benzodioxan-7-yl]benzamide,
N-[7-(4-methylpiperazin-1-yl)-2,3-dihydro-2-methylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide, or
N-[7-(4-methylpiperazin-1-yl)-2,3-dihydro-2,2-dimethylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
N-[7-(Piperazin-1-yl)-2,3-dihydro-2,2-dimethylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
4-Bromo-3-methyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydro-2,2-dimethylbenzofuran-5-yl]benzamide,
N-[7-(piperazin-1-yl)-2,3-dihydro-2-methylbenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
4-Bromo-3-methyl-N-[7-(4-methylpiperazin-1-yl)-2,3-dihydro-2-methylbenzofuran-5-yl]benzamide,
N-[7-(4-methylpiperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
N-[7-(Piperazin-1-yl)-2,3-dihydrobenzofuran-5-yl]-2'-methyl-4'-(5-methyl-1,2,4-oxadiazol-3-yl)biphenyl-4-carboxamide,
or a pharmaceutically acceptable salts thereof.

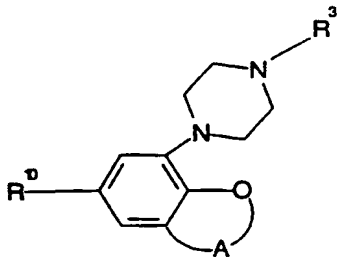
8. A process for the preparation of a compound of formula (I) which comprises

(a) reaction of a compound of formula (II):



(II)

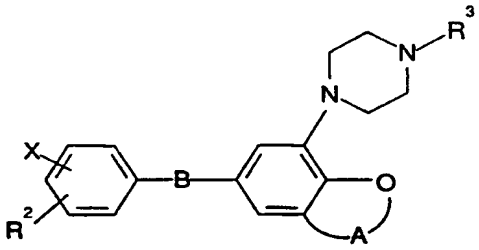
with a compound of formula (III):



(III)

in which R^1, R^2, R^3 and A are as defined in formula (I) and R^9 and R^{10} contain the appropriate functional group(s) necessary to form the B moiety;

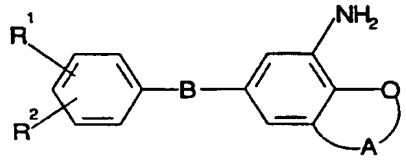
(b) reaction of a compound of formula (IV):



(IV)

in which R^2, R^3, A and B are as defined in formula (I) and X is a leaving group with a nucleophile R^1 where R^1 is as defined in formula (I); or

(c) reaction of a compound of formula (V):



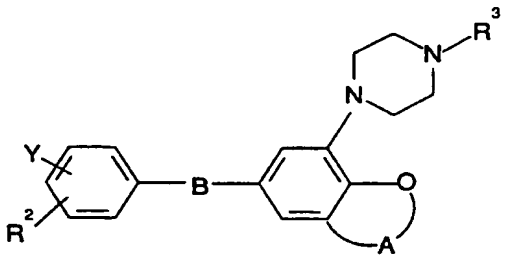
(V)

in which R^1, R^2, A and B are as defined in formula (I) with a compound of formula (VI):

$$R^3N(CH_2CH_2Hal)_2 \qquad (VI)$$

in which R^3 is as defined in formula (I) and Hal is halogen, or

(d) reaction of a compound of formula (VII):



(VII)

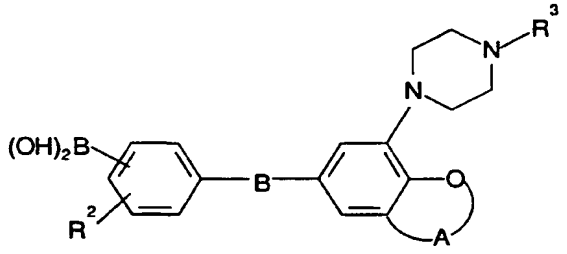
in which R^2, R^3, A and B are as defined in formula (I) and Y is halogen or a group $-OSO_2CF_3$ with a compound of formula (VIII):

$$R^1B(OH)_2$$

(VIII)

in which R^1 is as defined in formula (I), or

(e) reaction of a compound of formula (IX):



(IX)

in which R^2, R^3, A and B are as defined in formula (I) with a compound of formula (X):

$$R^1Y$$

(X)

in which R^1 is as defined in formula (I) and Y is as defined in formula (VII),

and optionally thereafter:

- converting a compound of formula (I) into another compound of formula (I)
- forming a pharmaceutically acceptable salt.

9. A compound according to any one of claims 1 to 7 for use in therapy.

10. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 in association with a pharmaceutically acceptable carrier or excipient.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 94/03387

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D307/79 C07D319/18 C07D405/12 C07D413/12 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 533 266 (GLAXO GROUP RESEARCH LTD.) 24 March 1993 cited in the application see claims ---	1-10
A	EP,A,0 533 267 (GLAXO GROUP RESEARCH LTD.) 24 March 1993 cited in the application see claims ---	1-10
A	EP,A,0 533 268 (GLAXO GROUP RESEARCH LTD.) 24 March 1993 cited in the application see claims ---	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 December 1994	22. 12. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

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INTERNATIONAL SEARCH REPORT

Int. onal Application No
PCT/EP 94/03387

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	JOURNAL OF MEDICINAL CHEMISTRY, vol.37, no.15, 22 July 1994, WASHINGTON US pages 2253 - 2257 J.W. CLITHEROW ET AL. 'Evolution of a novel series of ((N,N-Dimethylamino)propyl)- and piperazinylbenzanilides as the first selective 5-HT1D antagonists.' see the whole document ---	1-10
P,A	JOURNAL OF MEDICINAL CHEMISTRY, vol.37, no.17, 19 August 1994, WASHINGTON US pages 2761 - 2773 B.J. VAN STEEN ET AL. 'Structure-affinity relationship studies on 5-HT1A receptor ligands. Heterobicyclic phenylpiperazines with N4-aralkyl substituents.' see the whole document -----	1-10

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. onal Application No
PCT/EP 94/03387

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		JP-A-	6107649	19-04-94
		US-A-	5356893	18-10-94
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		CA-A-	2078507	19-03-93
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